1. Claims 61 and 63-73 are objected to due to informalities. Appropriate corrections have been made to incorporate the Examiner's suggestions. Applicants note, however, that such amendments are made to correct typographical errors only, and do not narrow the scope of the claims. Reconsideration and withdrawal of the objection is respectfully requested.

2. Claims 62, 72, and 73 are rejected under 35 U.S.C. 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants traverse this rejection.

The Examiner correctly indicates that a *patched* loss-of-function phenotype can be produced by mutations in other components of the *patched* signaling pathway, however, the Examiner incorrectly indicates that such a scenario is not accounted for in the specification.

Firstly, one of skill in the art will recognize that mutations at any point in a pathway can produce a mutant phenotype, a well established concept in developmental biology and genetics. The concept of epistatic analysis is founded on the idea that mutations at various points along a signaling pathway result in similar phenotypes. Similarly, the classification of genes into signaling pathways depends on both biochemical interactions among such genes, as well as genetic analyses indicating that mutations in these genes result in analogous effects. Thus, this concept is well established in the art, and need not be explicitly stated in the specification. According to the Guidelines for the Examination of Patent Applications, page 1106, column 1, "[t]he description need only describe in detail that which is new or not conventional." However, Applicants note that this idea was, in fact, explicitly described in the specification. In the Detailed Description of the Invention, Page 5, line 35-36, Applicants note that many human tumors can be characterized by loss of *patched* function, "such as that resulting from oncogenic mutations at the ptc locus, or other loss-of-function mutations which decrease ptc activity in the cell." Description of Applicants' results further illustrates their appreciation for this point. When discussing the role of *patched* signaling in BCNS, page 33, lines 11-16, Applicants note that mutations in other genes in the same signaling pathway (*fused*, *cubitus interruptus*, *protein kinase A*, and *costal2*) may modify the BCNS phenotype and be important in oncogenesis. Since

the ability of mutations at various points in a signaling pathway to result in a mutant phenotype is a fact implicit to one of skill in the art, and because Applicants provided explicit statements demonstrating an understanding of this concept and its relevance to the claimed invention, Applicants request reconsideration and withdrawal of this rejection.

3. Claims 61-73 are rejected under 35 U.S.C. 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, particularly for failing to enable for methods of identifying agents which are useful for treating an animal having a disorder characterized by loss of function of a *patched* gene. Applicants assert that the specification provides extensive support for the identification of agents useful in the treatment of animals. However to expedite prosecution, Applicants have amended the claims to restate the function of the agents identified in the claimed methods. Applicants point out that such amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope in a future application. Reconsideration and withdrawal of this rejection is respectfully requested.

4. Claims 62, 72, and 73 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite specifically for failing to define in the specification what constitutes a patched loss-of-function phenotype and how to measure partial reversal of this loss-of-function phenotype. Applicants respectfully traverse this rejection. These terms are defined and illustrated with a series of examples in the specification in sufficient detail that one of skill would readily comprehend the metes and bounds of the claimed subject matter.

Applicants define loss-of-function of a patched gene as mutations "which ultimately decrease or otherwise inhibit the ability of a cell to transduce patched-mediated signals, e.g., the cells may lose responsiveness to hedgehog induction." Detailed Description of the Invention, page 6. Contrary to the assertion of the prior Office Action, Applicants have clearly defined the loss-of- function phenotype in terms of the responsiveness of a single cell. Furthermore,

Applicants have provided many ways to assess a partial reversal of the patched loss-of-function phenotype. Two such examples are found on pages 9 and 20 of the specification where reversal or partial reversal of a patched loss-of-function phenotype can be monitored by measuring the ability of functional patched to antagonize hedgehog signaling. Therefore, any gene products known to be either activated or inhibited by patched activity, including Gli, PTHrP, TGF, Wnt, and others, can be assayed to measure patched activity.

Additionally, reversal of the patched loss-of-function phenotype can be monitored by ascertaining the characteristics of the cells characterized by the loss-of-function phenotype. Analysis of human tumors indicates that the loss-of-function of the patched tumor suppressor in a cell has oncogenic effects on that cell (see Detailed Description of the Invention, pages 5-6). The reduction or elimination of these characteristics can serve as a cellular criteria for evaluating the partial reversal of the patched loss-of-function phenotype. This technique is most elegantly demonstrated by Applicants' use of heterozygous patched loss-of-function mice (see pages 36-38). These mice have phenotypes similar to BCNS patients and exhibit an increased incidence of medulloblastomas. This example illustrates the cellular changes associated with loss-of-function of patched. Additionally, Applicants present data in which loss-of-function of patched in these tumors was measured quantitatively with respect to the expression of the patched responsive genes patched and gli (page 37, line 19). This description not only helps to define the loss-of-function phenotype, but also provides a method to quantify reversal or partial reversal of a patched loss-of-function phenotype by examining the change of gene expression of markers like patched and gli.

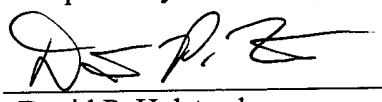
Applicants maintain that the terms "patched loss-of-function phenotype" and "partial reversal of patched loss-of-function phenotype" are described in the specification in sufficient detail to particularly point out the subject matter of this invention. The specification defines the terms in the context of the responsiveness of a single cell, and provides several methods to assess the reversal or amelioration of the loss-of-function phenotype. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

5. Claims 63-71 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. Applicants maintain that the claims, as written, definitively point out the claimed subject matter. However to expedite prosecution, Applicants have amended claims 63 and 72 to incorporate the Examiner's suggestions. Claim 64 was rejected for failing to recite the antecedent. Applicants respectfully request further clarification of this rejection, and will make appropriate corrections if indicated. In light of these amendments, Applicants request reconsideration and withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



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